REMARKS

Applicants respectfully request reconsideration of the present application in view of the reasons that follow.

I. Status Of The Claims

Claims 21 and 22 are pending in this application. Both claims were rejected under a double patenting rejection maintained from a previous action. *See* Office Action, page 3. In addition, claims 21 and 22 were newly rejected under 35 U.S.C. § 103(a). *See* Office Action, pages 4-5. Each ground is addressed below.

II. Provisional Double Patenting Rejection

Claims 21and 22 were provisionally rejected under the judicially-created doctrine of double patenting as being allegedly unpatentable over claims 33-35 of the co-pending U.S. Patent Application No. 08/340,664. *See* Office action, page 3.

Applicants respectfully defer a response to this rejection, if it is still applicable, until such time as allowable subject matter is indicated in the present application.

III. 35 U.S.C. § 103(a)

Claims 21 and 22 were rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Keutmann et al., *Biochemistry 17(26)*:5723-5729 (1978) ("Keutmann"), and Singh et al., *Nucleic Acids Res. 12(23)*:8927-8938 (1984) ("Singh"). *See* Office Action, page 4. Applicants respectfully traverse this ground for rejection.

A. Basis Of The Rejection

The Examiner stated that Keutmann teaches the sequence for human parathyroid hormone (hPTH), discloses that hPTH is only available in limited quantities from natural sources, and indicates that a supply would be useful for further study. *See* Office Action, page 4. The Examiner noted that Keutmann does not teach protein expression. *See* Office Action, page 4.

Continuing, the Examiner stated that Singh teaches a method of producing secreted proteins in yeast which results in the expression of intact active products with the complete sequence. *See* Office Action, page 4.

The Examiner concluded that one of ordinary skill in the art would have been motivated to make recombinant intact hPTH(1-84), with a reasonable expectation of success, using the method of Singh to make the product of Keutmann. *See* Office Action, page 5. Applicants respectfully request reconsideration and withdrawal of the rejection.

B. Basic Requirements Of a Prima Facie Case Of Obviousness

A proper rejection for obviousness under § 103 requires consideration of two factors: (1) whether the prior art would have suggested to one of ordinary skill in the art that they should make the claimed invention, and (2) whether the prior art would also have revealed that one of ordinary skill in the art would have had a reasonable expectation of success. MPEP § 2143. Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applicant's disclosure. *See In re Vaeck*, 947 F.2d 488, 493, 20 USPQ2d 1438 (Fed. Cir. 1991) (emphasis added). In the present case, the Examiner has failed to establish a *prima facie* case of obviousness for the reasons detailed below.

C. One Skilled In The Art Would Not Have A Reasonable Expectation of Success In Producing The Composition Of Keutmann By The Method Of Singh

In the present case, one skilled in the art would not have a reasonable expectation of success to recombinantly produce intact hPTH(1-84) in view of the widely acknowledged fragmentation of the peptide. MPEP § 2143.02. For example, Keutmann specifically note how those in the art recognized the "extensive fragmentation" of hPTH which occurs prior to extraction from tissue. *See* page 5727, col. 1, ¶ 4 (and references cited therein). In fact, Keutmann utilizes an strategy of extensive Edman degradation of multiple peptide subfragments to minimize the influence of heterogeneous samples of non-intact and intact hPTH peptides. *See, e.g.*, Figure 2 (showing filtration trace of a tryptic digest of hPTH).

If those skilled in the art recognize that hPTH undergoes "extensive fragmentation" *in vivo*, they would also recognize any recombinant expression method must also overcome this peptide degradation to produce biologically active, intact hPTH. Neither Keutmann nor Singh suggest or teach methods which overcome this well-known problem.

Moreover, Applicants previously presented evidence that those skilled in the art would not have a reasonable expectation of success to recombinantly produce intact hPTH(1-84) in yeast. For the Examiner's convenience, Applicants attach the preliminary amendment and declaration from related U.S. Patent Application No. 07/393,851 ("the '851 application"), which issued as U.S. Patent No. 5,010,010. *See* Attachments A and B, respectively.

In the '851 application, Applicants proffered the declaration of Dr. Janet Kurjan, an inventor of the yeast α-factor expression system. *See* Attachment B, ¶ 3. Dr. Kurjan noted, for example, the known "lack of success . . . in the expression, processing and secretion of heterologous peptides," Attachment B, ¶ 4, using the yeast expression system that she invented, *see* Attachment B, ¶ 2. This was the same yeast expression system used by Singh. *See* Singh, page 8928, line 6, and page 8938, reference 10.

In her declaration, Dr. Kurjan recognized the "known fragility" of hPTH to proteases. *See* Attachment B, ¶ 7. In addition, Dr. Kurjan remarked that "the very protease that is responsible for successfully cleaving the pro region of mating factor alpha" could also degrade the expressed hPTH protein. *See* Attachment B, ¶ 7. In contrast, Singh does not teach how to overcome the "known fragility" of hPTH. Accordingly, those skilled in the art would not have a reasonable expectation of success to recombinantly produce the composition of Keutmann by the method of Singh.

At best, the Examiner is using an improper "obvious to try" standard, arguing that it would have been obvious to a person of ordinary skill in the art to purify the composition of Keutmann from the method of Singh. However, "'obvious to try' has long been held to not constitute obviousness." *In re Deuel*, 34 USPQ2d 1210 (Fed. Cir. 1995).

D. The Teaching Of Høgset et al. and Kareem et al. Support A Finding Of Nonobviousness

The ability of *E. coli* to cleave hPTH has been documented and characterized in detail by Høgset et al., *J. Biol. Chem. 265*:7338-7344 (1990) ("Høgset") and Kareem et al., *Anal. Biochem. 204*:26-33 (1992) ("Kareem"). For example, Høgset and Kareem identify the amino acid residues at which the major cleavages occur and detail that N-terminally modified hPTH, presumably fMET-PTH, and non-intact hPTH were found biologically inactive. Both references provide strong evidence showing that hPTH expression in *E. coli* results in degradation of the intact hPTH peptide. *See* MPEP § 2143.02. Such evidence strongly supports a conclusion of nonobviousness. *See In re Rinehart*, 189 USPQ 143 (CCPA 1976). Accordingly, Applicants respectfully request withdrawal of this ground of rejection.

IV. Conclusion

The present application is now in condition for allowance. Favorable reconsideration of the application is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of

papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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